

A Biochemical Reaction Network with Multiple Functionalities

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Extended abstract

For the analysis of intracellular reaction networks, it is common practice to study semi-autonomous modules [1]. Here, we study an idealized module, which can only be influenced by the rest of the network through control of protein expression. The functionality of such a module depends on the concentrations of its constituent proteins. The same module may therefore behave differently in distinct cell types, which share the same global reaction network, but function in a different region of its state space.

Changes in protein expression may alter the functionality of a module in three ways: the module can either be switched on or off, it can be changed in a quantitative fashion or the qualitative functionality can be changed.

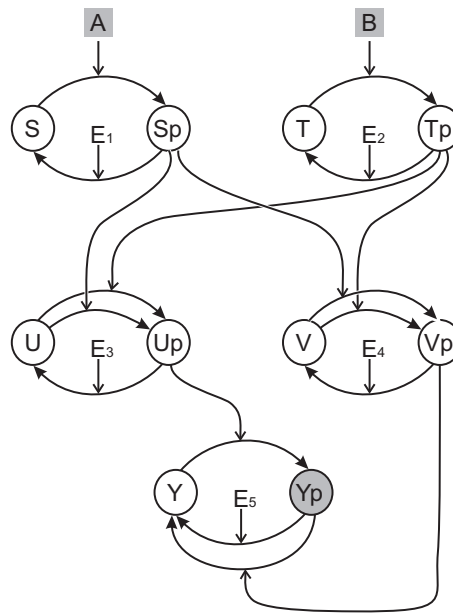


Figure 1: Reaction scheme of the network. System parameters $[E_1] \dots [E_5]$, S_{tot} , T_{tot} , U_{tot} , V_{tot} determine the response of $[Y_p]$ to input concentrations $[A]$ and $[B]$.

We illustrate the latter with a conceptual network of 5 phosphorylation cycles with 2 inputs $[A]$ and $[B]$ (Figure 1). Under the assumption of Michaelis-Menten kinetics, the equilibrium concentrations in a phosphorylation cycle are sigmoidal functions of the ratio of kinase and phosphatase concentrations, as described by Goldbeter and Koshland [2]. We consider the total concentration in each of the cycles as system parameters, which depend on the state of the global system. These concentrations are denoted by $S_{\text{tot}} = [S] + [S_p]$, etc. Also

the concentrations of enzymes $E_1 \dots E_5$ are regarded as system parameters. As there are only feed-forward connections, the entire network has only one equilibrium for given system parameters and inputs ($[A]$ and $[B]$).

In order to obtain more insight in the possible behaviors of the network, we focus on its possibilities as a logic gate. For the input we define concentrations below 0.5 as False and above 0.5 as True. We consider the equilibrium concentration of Y_p as the output of the network. Here, we limit ourselves to sets of system parameters for which $U_{\text{tot}} > 0$, $V_{\text{tot}} \gg U_{\text{tot}}$, $Y_{\text{tot}} = 1$, $[E_1] = [E_2] = 0.5$, $[E_3] \leq [E_4]/2$, $[E_5] \approx U_{\text{tot}}/2$. Under these restrictions, we can show that only two system parameters (S_{tot} and T_{tot}) have to be adjusted to obtain 8 different logic functions (see Figure 2). Transition effects at the borders between different functionalities are minimal when all Michealis constants are small ($K_m \leq 0.01$).

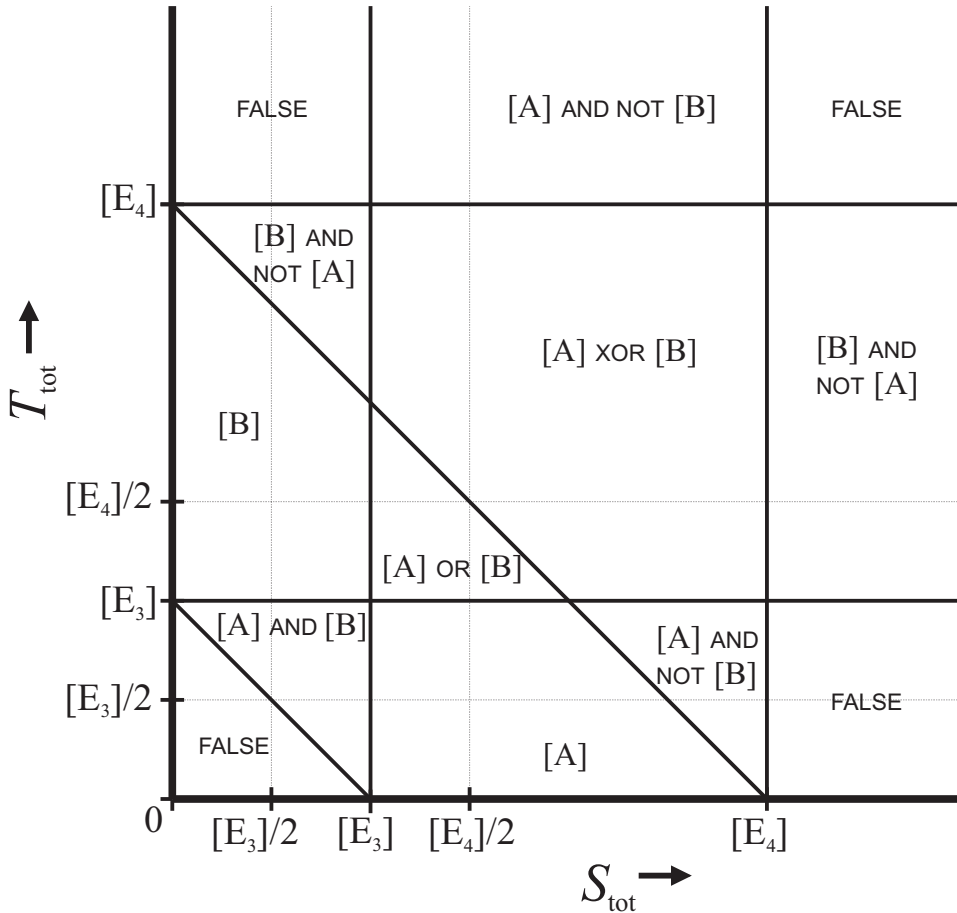


Figure 2: Network functionality (i.e., equilibrium concentration of Y_p as a function of $[A]$ and $[B]$) for combinations of S_{tot} and T_{tot} .

Our conceptual model is constructed from phosphorylation cycles, which are common building blocks in intracellular signaling networks [3]. This small network can already behave in at least 8 different ways, depending on how it is configured through the expression of proteins S and T. As real biological signaling networks are much larger, it seems likely to find similar phenomena in those networks. Some functional modules may for instance display different

functionalities among different cell types. Note that, from a modeling perspective, a purely qualitative approach would be insufficient to describe the functionalities of such a module.

Acknowledgements

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References

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